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Appeal Brief 1 of 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Hillman et al.

Title: NOVEL HUMAN INTEGRAL MEMBRANE PROTEIN

Serial No.:	09/207,161	Filing Date:	December 7, 1998
Examiner:	Carlson, K.	Group Art Unit:	1653

Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed December 22, 2000, herewith are three copies of Appellants' Brief on Appeal. Appellants hereby request a 3-month extension of time in order to file this Brief. Authorized fees include the statutory fee of $890.00 for a 3-month extension of time, as well as the $310.00 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner **finally** rejecting claims 1 and 11 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.), (Reel 8540, Frame 0003) who is the real party in interest herein.

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(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1 and 11
Claims allowed:	(none)
Claims canceled:	(none)
Claims withdrawn:	Claims 12-20
Claims on Appeal:	Claims 1 and 11 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

An Amendment after Final Rejection was filed on November 21, 2000. A subsequent Amendment After Final Rejection was filed on February 22, 2001. Neither of those Amendments was entered by the Examiner. Filed herewith is an additional Amendment After Final Rejection. As explained in this concurrently filed Amendment, the revisions to claim 1 reduce issues for appeal, at least, by rendering moot the rejection under 35 U.S.C. §102(a). Hence, it is believed that the concurrently filed Amendment After Final Rejection will be entered since it will place the application in better form for appeal by materially reducing and simplifying the issues under appeal.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed, *inter alia*, to polypeptides ("IMP-2") having chemical and structural homology to type II integral membrane proteins, and compositions containing those polypeptides, which have a variety of utilities including expression profiling, diagnosis of conditions or diseases characterized by expression of IMP-2, toxicology testing and drug discovery (see, e.g., the Specification at pages 27-28). The polypeptide has chemical and structural homology with murine

E25AMM (GI 624778; SEQ ID NO:3). In particular, IMP-2 shares approximately 40% overall identity with E25AMM, and has 49% identity and 71% similarity over the carboxy-terminal domains (residues 115-265 of IMP-2 and residues 111-261 of E25AMM). See, for example, Figure 2 and the Specification at pages 14-15. As illustrated by Figures 3 and 4, IMP-2 and E25AMM have similar hydrophobicity plots, particularly in the region of the presumable memberane spanning domain from residues 53-76 (Specification, page 14).

As explained on pages 1-2 of the Specification, the majority of known integral membrane proteins are transmembrane proteins which comprise an extracellular, a transmembrane, and an intracellular domain. Transmembrane proteins are typically embedded into the cell membrane by one or more regions comprising 15 to 25 hydrophobic amino acids which are predicted to adopt an α-helical conformation. Type II integral membrane proteins have a single transmembrane stretch of hydrophobic residues which is often located near the amino-terminus. The bulk of type II proteins comprise a carboxy-terminal domain which is located on the exterior side of the cell, and typically the carboxy-terminal domain comprises the active portion of the protein (e.g., the active site of an enzyme, the binding domain of a receptor).

The mouse *Itm2* gene which encodes the E25AMM protein, was found to be associated with chondro-osteogenic differentiation. *Itm2* is strongly expressed in mature osteoblasts and in early stages of secondary chondrogenesis. *Itm2* expression is not limited to chondro-osteogenic tissues as it is expressed in 1) heart, brain (choroid plexus), renal cortex, and the crypts of the small intestine (weak expression) and in 2) skin (stratum corneum), hair follicles and the acini of exocrine glands (strong expression) (Deleersnijder W. et al. (1996) J. Biol. Chem. 271:19475). (See Specification, for example, pages 1-2).

The expression of IMP-2 is described, for example, in the Specification at page 15:

> Northern analysis (Fig. 5) shows the expression of IMP-2-encoding sequences in various libraries, at least 24% of which are cancerous or immortalized and at least 17% of which are involved with the immune response, including inflammatory and/or autoimmune disease (e.g., rheumatoid synovium, ulcerative colitis, Crohn's disease, primary biliary cirrhosis). Of particular note is the expression of IMP-2 mRNA in brain tumor (7/214), prostate tumor (6/214), breast tumor (3/214) and bladder tumor

(3/214) libraries. This pattern of expression demonstrates that IMP-2 serves as a marker for cancerous cells, particularly brain and prostate tumor cells. In addition to its expression in a variety of tumors, IMP-2 is highly expressed in adult liver and fetal spleen and thus serves as a marker for these tissues.

As is demonstrated in Fig. 5, IMP-2 cDNA is strongly expressed in normal adult liver (>10% abundance; see LIVRNOT01 and LIVRNOM01 libraries) and its expression decreases precipitously in abnormal liver tissues, including primary biliary cirrhosis (see LIVRBCT01 library; 3.5% abundance) and liver tumors (see LIVRTUT01 library; 0.03% abundance). Thus, decreased or low level (i.e., less than about 50% the level seen in normal or disease-free, liver tissue) expression of IMP-2 in liver tissue serves as an indicator of liver disease, including liver cancer. A similar decrease in IMP-2 transcripts is observed when normal lung and lung tumors are compared; lung tumors show about a 50% decrease in IMP-2 transcript abundance as compared to normal adult lung (Fig. 5). Thus, decreased or low level expression of IMP-2 in lung tissue serves as an indicator of lung tumors. (Specification page 15, lines 5-23, and Figure 5).

(6) THE FINAL REJECTIONS

Claims 1 and 11 stand rejected under 35 U.S.C. § 102(a) allegedly for being anticipated by Delleersnijder et al., (1996; J. Biol. Chem. 271:19475-19482) (Office Action of September 25, 2000, Paper No. 15, page 7). The Examiner alleges in particular that:

- ". . . Deleersnijder et al. teach a E24AMM protein comprising fragments of SEQ ID NO:1. Therefore, Deleersnijder et al. teach biologically active fragments and immunological fragments of SEQ ID NO:1."

Claims 1 and 11 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the claimed invention was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Office Action of September 25, 2000, Paper No. 15, page 6). The Examiner alleges in particular that:

- "The Specification does not teach naturally occurring amino acid sequence having at least 90% identity to an amino acid sequence of SEQ ID NO:1. Therefore, one skilled in the art would

not know what this naturally occurring sequence would look like, or if the sequence represents a functional protein."

Claims 1 and 11 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. (Office Action of September 25, 2000, Paper No. 15, pages 2-3). The Examiner alleges in particular that:

- ". . . the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility" (Office Action, Paper No. 15, page 2).
- ". . . since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility . . . one skilled in the art clearly would not know how to use the claimed invention" (Office Action, Paper No. 15, page 3).

(7) ISSUES

1. Whether claims 1 and 11 are anticipated under 35 U.S.C. §102(a) by Deleersnijder et al. (J. Biol. Chem., 271:19475-19482, 1996).

2. Whether claims 1 and 11 satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

3. Whether claims 1 and 11 meet the utility requirement of 35 U.S.C. § 101.

4. Whether claims 1 and 11 satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, *i.e.*, would the Specification enable one of ordinary skill in the art to make and use the claimed sequences, *e.g.*, in toxicology testing, drug development, and the diagnosis of disease.

(8) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

All of the claims on appeal are grouped together.

As to Issue 4

All of the claims on appeal are grouped together.

(9) APPELLANTS' ARGUMENTS

Issue 1 – Whether claims 1 and 11 are anticipated under 35 U.S.C. § 102(b) by Deleersnijder et al.

Claims 1 and 11 stand rejected under 35 U.S.C. 102(a) as being anticipated by Deleersnijder et al.. According to the Examiner, "Deleersnijder et al. teach a E24AMM protein comprising fragments of SEQ ID NO:1. Therefore, Deleersnijder et al. teach biologically active fragments and immunological fragments of SEQ ID NIO:1." However, Deleersnijder et al has no disclosure that the polypeptide described in that document contains "biologically active fragments and immunological fragments of SEQ ID NO:1." Nevertheless, in the interest of simplifying issues for this appeal, the "fragment language" has been deleted from claim 1 by the Amendment filed concurrently herewith. Hence, the rejection over Deleersnijder et al has been rendered moot.

Accordingly, reversal of this rejection is requested.

Issue 2 – Whether claims 1 and 11 meet the written description requirement of 35 U.S.C. § 112, first paragraph

Claims 1 and 11 meet the written description requirement of 35 U.S.C. § 112, first paragraph, with respect to the recitation of polypeptides comprising a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of biologically active fragments and immunogenic fragments of SEQ ID NO:1

The Office Action has asserted that the Specification does not provide an adequate written description of biologically active fragments and immunogenic fragments of SEQ ID NO:1. Such, however, is not the case.

At pages 13-15, the Specification describes the polynucleotide of SEQ ID NO:2 and the polypeptide encoded by that polynucleotide, *i.e.*, SEQ ID NO:1, and chemical and structural characteristics thereof. The polypeptide and fragments thereof can be produced by either recombinant means (see, *e.g.*, the Specification at pages 16-27) or by chemical synthesis (see, *e.g.*, the Specification at page 20, lines 13-20; and page 27, lines 17-23). Polynucleotides can also be synthesized by chemical methods (see, *e.g.*, the specification at page 20, lines 13-15).

Note that at page 8, lines 11-12, biologically active is defined as "a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule" and immunologically active" is defined as "the capability of the natural, recombinant, or synthetic IMP-2, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies." Specific binding is further defined at page 12 as meaning that:

> . . . in reference to the interaction of an antibody and a protein or peptide, mean[s] that the interaction is dependent upon the presence of a particular structure (i.e., the antigenic determinant or epitope) on the protein; in other words, the antibody is recognizing and binding to a specific protein structure rather than to proteins in general. For example, if an antibody is specific for epitope "A", the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount of labeled A bound to the antibody.

Methods of producing specifically binding antibodies are described, for example, at pages 29-30. In this regard, note page 29, lines 19-25 which describes fragment sizes of IMP-2 (i.e., SEQ ID NO:1) for raising antibodies. See also page 51 which describes the production of antibodies to fragments of IMP-2, including the description of how to identify appropriate immunogenic sites of IMP-2:

> The amino acid sequence deduced from SEQ ID NO:2 is analyzed using DNASTAR software (DNASTAR Inc) to determine regions of high immunogenicity, and a

> corresponding oligopolypeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is described by Ausubel et al. (supra), and others. (Specification at page 51, lines 13-17)

Furthermore, the Specification describes at page 50, line 4 to page 51, line 8, methods for demonstrating biological activity of IMP-2 proteins.

Given the "blueprint" provided by SEQ ID NO:1, and the detailed guidance set forth by the Specification, the structure of fragments of SEQ ID NO:1 is apparent and there is no need to explicitly list the sequences of the numerous possible fragments. Such a list would just needlessly clutter the Specification.

Nevertheless, in the interest of simplifying issues for this appeal, the "fragment language" has been deleted from claim 1 by the Amendment filed concurrently herewith. Hence, issues pertaining to an adequate written description of biologically active fragments and immunogenic fragments of SEQ ID NO:1 have been rendered moot.

B. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1

The Office Action (Paper No. 15, page 6) further asserts that "[t]he specification does not teach naturally occurring amino acid sequences having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1. Therefore, one skilled in the art would not know what this naturally occurring sequence would look like, or if the sequence represents a functional protein." However, the subject matter encompassed by the claims is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 1 recites a polypeptide comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1."

The amino acid sequence of SEQ ID NO:1 is explicitly disclosed in the Specification. See, for example, Figure 1. One of skill in the art would know how to provide polynucleotide sequences encoding SEQ ID NO:1 as well as complements thereof. In this regard, the Specification also explicitly

discloses the particular polynucleotide species of SEQ ID NO:2, which encodes the amino acid sequence of SEQ ID NO:1 (see Figure 1). Similarly, one of skill in the art would recognize polynucleotide sequences encoding variants of SEQ ID NO:1. The Specification further describes, *e.g.*, at page 15, lines 24-27, naturally-occurring polypeptide variants of IMP-2 (i.e., SEQ ID NO:1). Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are relevant to "protein claims" by virtue of the capability of DNA to encode protein) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. A substantially purified polypeptide comprising . . . b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1 . . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the claimed polypeptides. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it

would add to the structural characterization of the claimed polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims to nucleic acids and polypeptides. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being highly variant, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078, of record). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significane of alignments, as Brenner et al., further report that ≥ 40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076).

The present application is directed, *inter alia*, to type II integral membrane proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as type II integral membrane proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites polypeptides comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 266 amino acid residues). This variation is far less than that of all potential type II integral membrane

proteins related to SEQ ID NO:1, i.e., those type II integral membrane proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

The case of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) provides further support for concluding that the polypeptide genus defined by the present claims complies with the written description requirement. As discussed above, certain claims of U.S. Patent No. 4,652,525 were found invalid for failing to satisfy the written description requirement. The *Lilly* case, however, also considered U.S. Patent No. 4,431,740. While there is a discussion in *Lilly* of issues of infringement and enforceability of the claims of the '740 patent, there is no written description analysis of the claims of the '740 patent. However, there was no holding of invalidity of any claim of the '740 patent. Thus, the claims of the '740 patent are presumed to satisfy the written description of 35 U.S.C. §112. See 35 U.S.C. §282. Now consider, for example, claim 4 of the '740 patent, which reads as follows:

> 4. A DNA transfer vector comprising a deoxynucleotide sequence coding for human pre-proinsulin consisting essentially of a plus strand having the sequence:

5'-$_{-24}$ GCL$_{-23}$ X$_{-22}$ TY$_{-22}$ TGG$_{-21}$ ATG$_{-20}$ W$_{-19}$ GZ$_{-19}$ X$_{-18}$ TY$_{-18}$ X$_{-17}$ TY$_{-17}$ CCL$_{-16}$ X$_{-15}$TY$_{-15}$ X$_{-14}$ TY$_{-14}$ GCL$_{-13}$ X$_{-12}$ TY$_{-12}$ X$_{-11}$ TY$_{-11}$ GCL$_{-10}$ X$_{-9}$ TY$_{-9}$ TGG$_{-8}$ GGL$_{-7}$ CCL$_{-6}$GAK$_{-5}$ CCL$_{-4}$ GCL$_{-3}$ GCL$_{-2}$ GCL$_{-1}$ TTK$_{1}$ GTL$_{2}$ AAK$_{3}$ CAJ$_{4}$ CAK$_{5}$ X$_{6}$ TY$_{6}$ TGK$_{7}$ GGL$_{8}$ QR$_{9}$ S$_{9}$ CAK$_{10}$ X$_{11}$ TY$_{11}$ GTL$_{12}$ GAJ$_{13}$ GCL$_{14}$ X$_{15}$ TY$_{15}$ TAK$_{16}$ X$_{17}$ TY$_{17}$ GTL$_{18}$ TGK$_{19}$ GCL$_{20}$ GAJ$_{21}$ W$_{22}$ GZ$_{22}$ GCL$_{23}$ TTK$_{24}$ TTK$_{25}$ TAK$_{26}$ ACL$_{27}$ CCL$_{28}$ AAJ$_{29}$ ACL$_{30}$ W$_{31}$ GZ$_{31}$ W$_{32}$ GZ$_{32}$ GAJ$_{33}$ GCL$_{34}$ GAJ$_{35}$ GAK$_{36}$ X$_{37}$ TY$_{37}$ CAJ$_{38}$ GTL$_{39}$ GGL$_{40}$ CAJ$_{41}$ GTL$_{42}$ GAJ$_{43}$ X$_{44}$ TY$_{44}$ GGL$_{45}$ GGL$_{46}$ GGL$_{47}$ CCL$_{48}$ GGL$_{49}$ GCL$_{50}$ GGL$_{51}$ QR$_{52}$ S$_{52}$ X$_{53}$ TY$_{53}$ CAJ$_{54}$ CCL$_{55}$ X$_{56}$ TY$_{56}$ GCL$_{57}$ X$_{58}$ TY$_{58}$ GAJ$_{59}$ GGL$_{60}$ QR$_{61}$ S$_{61}$ X$_{62}$ TY$_{62}$ CAJ$_{63}$ AAJ$_{64}$ W$_{65}$ GZ$_{65}$ GGL$_{66}$ ATM$_{67}$ GTL$_{68}$ GAJ$_{69}$ CAJ$_{70}$ TGK$_{71}$ TGK$_{72}$ ACL$_{73}$ QR$_{74}$ S$_{74}$ ATM$_{75}$ TGK$_{76}$ QR$_{77}$ S$_{77}$ X$_{78}$ TY$_{78}$ TAK$_{79}$ CAJ$_{80}$ X$_{81}$ TY$_{81}$ GAJ$_{82}$ AAK$_{83}$ TAK$_{84}$ TGK$_{85}$ AAK$_{86}$ TAGACGCAGCCCGCAGGCAGCCCCCCACCCGCCGCCTCCTGCACCGAGAGAGATGGA ATAAAGCCCTTGAACCA GC polyA-3'

> wherein
>
> A is deoxyadenyl,
>
> G is deoxyguanyl,
>
> C is deoxycytosyl,
>
> T is thymidyl,

J is A or G;

K is T or C;

L is A, T, C, or G;

M is A, C or T;

X_n is T or C if Y_n is A or G; and C if Y_n is C or T;

Y_n is A, G, C or T if X_n is C, and A or G if X_n is T;

W_n is C or A if Z_n is G or A, and C if Z_n is C or T;

Z_n is A, G, C or T if W_n is C, and A or G if W_n is A;

QR_n is TC if S_n is A, G, C or T, and AG if S_n is T or C;

S_n is A, G, C or T if QR_n is TC, and T or C if QR_n is AG; and, script numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

Claim 4 of the '740 patent recites a DNA sequence which includes the coding region for human pre-proinsulin; in particular, the 330 nucleotide bases from codon GCL_{-23} through codon AAK_{86} code for human pre-proinsulin. As can be seen from the claim language, claim 4 of the '740 patent sets forth a DNA structure with numerous variant positions. Of the 330 nucleotides in the coding region for human pre-proinsulin, 141 are potentially variant positions within the structure defined by claim 4. Thus, claim 4 of the '740 patent defines a DNA which potentially is only 57% identical (189/330 x 100% = 57%) to the single species of human pre-proinsulin actually sequenced in the '740 patent. See Example 1 and Figure 2. As discussed above, the present claims encompass naturally-occurring polypeptide variants which have at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1. Clearly, then, the genus variation of the present claims is less than that of claim 4 of the '740 patent.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of January 31, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is not "highly variant," as evidenced by Brenner et al and

consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, the Specification provides an adequate written description of the claimed subject matter, and reversal of this rejection is therefore requested.

Issue 3 – Whether the claims meet the utility requirement of 35 U.S.C. § 101

The rejection of claims 1 and 11 is improper, as the claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The inventions at issue are polypeptide sequences corresponding to a gene that is expressed in several specific tissues. Furthermore, as disclosed in the specification on page 15, lines 5-17, and lines 20-22:

> Northern analysis (Fig. 5) shows the expression of IMP-2-encoding sequences in various libraries, at least 24% of which are cancerous or immortalized and at least 17% of which are involved with the immune response, including inflammatory and/or autoimmune disease (e.g., rheumatoid synovium, ulcerative colitis, Crohn's disease, primary biliary cirrhosis). Of particular note is the expression of IMP-2 mRNA in brain tumor (7/214), prostate tumor (6/214), breast tumor (3/214) and bladder tumor (3/214) libraries. This pattern of expression demonstrates that IMP-2 serves as a marker for cancerous cells, particularly brain and prostate tumor cells. In addition to its expression in a variety of tumors, IMP-2 is highly expressed in adult liver and fetal spleen and thus serves as a marker for these tissues.
>
> As is demonstrated in Fig. 5, IMP-2 cDNA is strongly expressed in normal adult liver (>10% abundance; see LIVRNOT01 and LIVRNOM01 libraries) and its expression decreases precipitously in abnormal liver tissues, including primary biliary cirrhosis (see LIVRBCT01 library; 3.5% abundance) and liver tumors (see LIVRTUT01 library; 0.03% abundance) . . . A similar decrease in IMP-2 transcripts is observed when normal lung and lung tumors are compared; lung tumors show about a 50% decrease in IMP-2 transcript abundance as compared to normal adult lung (Fig. 5).

As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Any of these uses meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If

and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The rejection fails to demonstrate either that the Appellants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be overturned.

There is, however, an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law. These inconsistencies are discussed separately below.

I. Use of the claimed polypeptides for diagnosis of conditions or diseases characterized characterized by expression of IMP-2, for toxicology testing, and for drug discovery, are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There is a "well-established" use for the claimed invention, there are specific practical and beneficial uses for the invention, and those uses are substantial. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Likewise, proteome expression profiling techniques have been developed in which the

expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.,* Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, which is used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra.*

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them.

There are numerous additional uses for the information made possible by expression profiling. Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and

lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

B. The use of IMP-2 polypeptides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is not conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no

dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the protein expressed by the claimed nucleic acid or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

1. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § I). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil Co. v. Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is known to be useful. It is not just a random sequence of speculative use. Because it is expressed in humans, a person of ordinary skill in the art would know how to use the claimed polypeptide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the

polynucleotide or the protein it encodes actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of type II integral membrane proteins. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as cancer, affects the expression of type II integral membrane proteins and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed polypeptide sequences could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptide remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the specific functions of the proteins.

2. A patent applicant may specify a utility that applies to a broad class of inventions

The fact that the claimed invention is a member of a broad class (such as DNA sequences or the proteins they encode expressed in humans) that includes sequences other than those claimed that also have utilities in toxicology testing, drug discovery, disease diagnosis, etc. does not negate utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that

include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of

this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, **all** isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressable (i.e., which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences actually expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Type II integral membrane proteins, like interleukins, GPCRs and fishing rods, is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, the claimed type II integral membrane protein, is expressed by humans, and can be used as a tool for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of type II intergral membrane proteins in humans, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless type II integral membrane proteins. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

C. Because the use of IMP-2 polypeptides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

The claimed invention's use as a tool for toxicology testing is just such a practical, real-world use. The PTO nonetheless rejected the claims at issue on the ground that the use of an invention as tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. In fact, the PTO issues patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the CCPA held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at

940, 945 ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include: assessing IMP-2 expression in the diagnosis of disease when compared to a normal or standard profile for IMP-2 expression (see specification page 15, lines 14-20) and the use of IMP-2, its catalytic or immunogenic fragments or oligopeptides thereof, can be used for screening libraries of compounds in any of a variety of drug screening techniques (specification page 41, lines 11-13).

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

II. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this procedure. *See* Revised Interim Guidelines at ¶ ¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt

that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the present case, the specification (pages 14-15) clearly discloses that the claimed IMP-2 has:

> . . . the amino acid sequence of SEQ ID NO:1, as shown in Fig. 1. IMP-2 is 266 amino acids in length and contains nine cysteine residues (i.e., C_{38}, C_{54}, C_{56}, C_{57}, C_{89}, C_{164}, C_{223}, C_{248}, and C_{265}). In addition to providing sites for disulfide bond formation, the cysteine residues provide potential sites for palmitoylation. Five of the nine cysteine residues found in human IMP-2 are conserved in location with cysteine residues found in the mouse E25AMM protein (i.e., C_{56}, C_{164}, C_{223}, C_{248}, and C_{265} of IMP-2). The human IMP-2 of the present invention contains numerous potential O-linked glycosylation sites (*i.e.*, serine and threonine residues). IMP-2 has a single potential N-linked glycosylation site (*i.e.*, Asn-X-Ser/Thr) (*i.e.*, N_{170}) which is conserved in location with the single N-linked glycosylation site found in the mouse E25AMM protein (Deleersnijder et al., supra). In addition, the human IMP-2 of the present invention contains numerous potential phosphorylation sites (*i.e.*, typically the hydroxyl groups of serine, threonine and tyrosine residues although asparagine, histidine and lysine residues may also be phosphorylated), including a potential site for phosphorylation by cAMP-dependent protein kinase (*e.g.*, R-X-S/T) (*i.e.*, T_{236}).
>
> The IMP-2 protein of the present invention, like the mouse E25AMM protein, has an acidic isoelectric point (pI) (IMP-2 has a pI of 4.86 and E25AMM has a pI of 5.41). In addition, the IMP-2 protein of the present invention, like the mouse E25AMM protein, has a high content of leucine and isoleucine residues (IMP-2 contains 9% leucine and 9% isoleucine; E25AMM contains 10.2% leucine and 8% isoleucine).
>
> IMP-2 contains a stretch of hydrophobic amino acid residues at positions 53-76 which presumably forms the membrane spanning domain. As illustrated by Figs. 3 and 4, IMP-2 and E25AMM have similar hydrophobicity plots.
>
> IMP-2 has chemical and structural homology with the mouse E25AMM protein (GI 624778; SEQ ID NO:3) (Deleersnijder et al., supra). In particular, IMP-2 and E25AMM share 39.8% identity overall and 49% identity and 71% similarity over the carboxy-terminal domains (residues 115-265 of IMP-2 and residues 111-261 of E25AMM). A pair of residues are said to be similar if they represent conservative substitutions. Figure 2 provides an alignment between the amino acid sequences of SEQ ID NOS:1 and 3.

The only evidence of record shows that a person of ordinary skill in the art would not doubt that IMP-2 is in fact a type II integral membrane protein, which is known to have a specific utility.

By ignoring the "reasonable correlation" requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Appellants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Appellants to rebut.

III. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard.

Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus, the Training Materials cannot be applied consistently with the law.

Issue 4 – Whether the claims meet the enablement requirement of 35 U.S.C. § 112, first paragraph

To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

(10) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity" as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"[1] to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specification as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial, and credible utilities. The "utility" rejections are, therefore, improper and should be reversed.

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[1] "The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

The written description and anticipation rejections should also be reversed, based on at least the arguments presented above.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

Respectfully submitted,

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APPENDIX

Claims involved in the Appeal:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1, and

b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence of SEQ ID NO:1,

11. A composition comprising an effective amount of a polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.